REMARKS

Claims 1-44, 46-66, 68, and 69 are pending in the application, claims 45 and 67 having been cancelled. Claims 1, 5, 47, and 52 have been amended. Support for the amendments can be found in the specification at, e.g., page 4, lines 24-26, and page 9, lines 30-37. No new matter has been added by these amendments.

Election/Restriction

Claim 67 has been cancelled. Claims 1 and 5 have been amended to remove the non-elected subject matter of nucleic acids encoding polyepitope polypeptides containing tumor antigen epitopes and methods of using such nucleic acids.

35 U.S.C. § 112, 1st Paragraph

On pages 3-7 of the Office Action, the Examiner rejected claims 60-66 as allegedly not enabled. Claims 60-66 are directed to methods of eliciting an immune response in a mammal by administering the nucleic acid of claim 1 to the mammal. At page 3 of the Office Action, the Examiner acknowledged that the claimed methods are enabled for three embodiments: (1) a nucleic acid encoding a hybrid polypeptide containing a "targeting signal sequence" and the recited segments; (2) administering the nucleic acid to a mammal intramuscularly or directly at a target tissue site containing antigen presenting cells; and (3) administering the nucleic acid to a mammal in a microsphere containing a polymeric matrix or shell. The Examiner asserted that the full scope of the claimed methods is not enabled.

Applicants respectfully submit that one of ordinary skill in the art, as of the filing date of the application, could have performed the full scope of the claimed methods without undue experimentation, from the disclosure in the specification coupled with information known in the art.

At page 4 of the Office Action, the Examiner stated that claims directed to the use of a signal sequence other than a target signal sequence are not enabled. A "signal sequence," which is a type of "targeting signal," is located at the amino terminal of a protein and directs the protein into the ER during translation. The terms "signal sequence" and "signal peptide" are used

interchangeably in the specification and by those of skill in the art. The specification provides extensive teachings on the use of such a signal sequence linked to a hybrid polypeptide. This clarification of the meaning of the phrase "signal sequence" is expected obviate the Examiner's rejection based upon the use of this phrase.

A person of ordinary skill in the art at the time the application was filed would have been able to carry out the claimed methods by using means not limited to only intramuscular administration or direct administration to a target tissue site containing antigen presenting cells, as suggested by the Examiner. The teachings of the specification combined with the knowledge in the art enabled the skilled artisan to use the nucleic acids in a variety of different administration methods. Additional standard routes of administration include the following: intravenous, intraarterial, intrathecal, intradermal, intraperitoneal, intranasal, intrapulmonary, intraocular, intravaginal, intrarectal, and subcutaneous (see specification at page 31, lines 21-23). Such administrations can be either local or systemic. Since the nature of the invention relates to immunostimulation, a skilled artisan would have understood that the immune system can be stimulated at one location and a subsequent anti-pathogen immune response can be effected at a distant site (e.g., following the migration of activated T cells to a distal site). A skilled artisan would have understood that such an immune response could be elicited using the claimed nucleic acids by means in addition to intramuscular administration or direct administration to a target tissue site.

With respect to the Examiner's comments regarding mucosal routes of administration, methods were available at the time of filing of the present application to enhance the transport of biomolecules across the gastrointestinal barrier. For example, it was known that bacterial invasion proteins can be used in carrier systems (e.g., microparticles) to obtain such transport (see, e.g., WO 96/13250). Accordingly, the skilled artisan was aware of methods that would enhance the efficiency of mucosal administration of the claimed nucleic acids.

The skilled artisan would have been able, at the time of filing of the present application, to practice the claimed methods using means of delivering a nucleic acid to a cell in addition to using a microsphere containing a polymeric matrix or shell. Other well-known methods of delivering nucleic acids to a cell include, but are not limited to, incorporating nucleic acids into vehicles such as liposomes or immune-stimulating complexes (ISCOMS) or delivering nucleic

acids with naturally occurring polymers, synthetic polymers, biopolymers, cationic lipids, condensing agents, dendrimers, other biomaterials, oil-containing adjuvants, and other adjuvants such as QS21 or saponin (see specification at page 13, lines 22-29). In addition, nucleic acids can be delivered to a cell as "naked DNA," without a delivery vehicle (other than an aqueous solution).

In light of these comments applicants submit that a skilled artisan would have been able to practice the full scope of the claimed methods without undue experimentation at the time the application was filed. Accordingly, applicants request that the Examiner withdraw the rejection.

35 U.S.C. § 112, 2nd Paragraph

On page 7 of the Office Action, the Examiner rejected claims 1-66, 68, and 69 as allegedly indefinite in the use of the phrase "signal sequence." According to the Examiner, "it is not apparent as to that exactly the 'signal' is intended for the structural and/or function of the claimed nucleic acid sequences."

Applicants respectfully traverse the rejection. According to the specification, a "targeting signal" is a peptide sequence that "can direct the polyepitope polypeptide to endoplasmic reticulum (ER), the golgi, the nucleus, a lysosome, a class II peptide loading compartment, or an endosome." The specification further describes a "signal sequence" as a type of targeting signal that directs proteins into the ER during translation. The terms "signal sequence" and "signal peptide" are used interchangeably in the specification and by those of skill in the art. In light of these comments, applicants request that the Examiner withdraw the rejection.

35 U.S.C. § 103(a)

On pages 7-9 of the Office Action, the Examiner rejected claims 1-66, 68, and 69 as allegedly obvious over either Hedley et al., U.S. Patent No. 5,783,567 ("Hedley") or Urban et al., U.S. Patent No. 6,183,746 ("Urban"), taken with either Boursnell et al., U.S. Patent No. 5,719,054 ("Boursnell") or Boursnell, Edwards et al., U.S. Patent No. 6,004,557 ("Edwards"), Dillner et al., U.S. Patent No. 5,932,412 ("Dillner"), and Bleul et al., U.S. Patent No. 5,753,233 ("Bleul"). According to the Examiner,

[b]oth Hedley *et al.* or Collins *et al.* [Urban] teach a method of eliciting an immune response in a mammal, the method comprising administering to the mammal an effective amount of microspheres comprising a polymeric matrix or shell and a nucleic acid encoding a trafficking signal sequence and polyepitopes of HPV, wherein the nucleic acid encodes a hybrid polypeptide comprising a targeting signal sequence and polyepitopes of naturally occurring pathogenic proteins, wherein the epitopes are either contiguous or are separated by a spacer amino acid or spacer peptide:

and wherein the nucleic acid encodes at least a HPV epitope of at least 11 amino acids in length (Hedley *et al.*, e.g., columns 2, 6, 13, 14, 61-64) and Collins *et al* [Urban], entire document).

Both Hedley *et al.* and Collins *et al.* [Urban] do not teach the specific combination of HPV epitopes designated as SEQ ID NOS: 66, 69, 152, and 154 for use in the making the HPV polyepitope encoding plasmid containing microspheres.

However, at the time the invention was made, the concept of employing HPV polyepitope encoding vector is well recognized in the prior art as exemplified in Boursnell *et al.* (entire document, specially columns 2, 3, 5, and 8). In fact Boursnell *et al.* teach the HPV epitopes comprising SEQ ID NOS: 66, 69, 152, and 154 in SEQ ID NOS: 9 (comprising SEQ ID NO: 69), 10 (comprising both SEQ ID NOS 66 and 152) and 13 (comprising SEQ ID O: 154). Furthermore, Edwards *et al.* (US Pat No. 6,004,557), Dillner *et al.* (US Pat No. 5,932,412) and Bleul *et al.* (US Pat NO. 5,753,233) are exemplified references that discloses the immunoreactive HPV epitopes of SeQ ID NOS 66, 69, 152, and 154, respectively in SEQ ID NO: 12 (Edwards *et al.*), SEQ ID NO: 157 (Dillner *et al.*) SEQ ID NO: 2 (Bleul *et al.*) and SEQ ID NO: 61 (Dillner *et al.*).

It would have been obvious for one of ordinary skill in the art at the time the invention was made to have employed any combination of HPV epitopes available in the prior art such as those disclosed in Boursnell *et al.* and or in Boursnell *et al.* taken with Edwards *et al.* (US Pat No. 6,004,557), Dillner *et al.* (US Pat No. 5,932,412) and Bleul *et al.* (US Pat NO. 5,753,233) in the DNA immunization methods of Hedley *et al.* or Collins *et al.* [Urban] so as to increase an immune response against HPV in any target mammal. One of ordinary skill in the art would have been motivated to have employed the combination as recited in the elected species because the combination of the known epitopes are minor modifications and expected to provide addictive [sic] effect in increasing an immune response against HPV in a target mammal, as taught by Hedley *et al.*, Collins *et al.* [Urban] and Boursnell *et al.*, and because Boursnell *et al.*, Edwards, Dillner *et al.* and Bleul *et al.* all teach that the epitopes comprising SEQ ID NOS

66, 69, 152 and 154 are immunoreactive to antibodies against HPV.

Applicants respectfully traverse the rejection in light of the following comments.

The claimed invention is directed to a nucleic acid encoding a hybrid polypeptide that contains one or more segments, each segment having the sequence of a portion of a naturally occurring protein of a pathogenic agent. Each segment contained in the encoded hybrid polypeptide contains at least two epitopes (an epitope is a peptide that binds to the binding groove of an MHC molecule or the antigen-binding region of an antibody). The segments can be arranged in tandem in the hybrid polypeptide, optionally including spacer amino acids between segments, and can be linked to a signal sequence.

A hybrid polypeptide encoded by the claimed nucleic acid is particularly useful for generating an immune response, as each segment of the polypeptide contains multiple peptide epitopes that can be recognized by the immune system and trigger an immune response against the pathogenic agent. Having a plurality of epitopes within a single segment has several advantages. First, it can help augment the diversity of an immune response in an individual, as the immune system can be simultaneously activated to recognize two or more targets. Second, it can increase the likelihood that a segment will contain at least one epitope that will stimulate the immune system of a given individual. For example, a protein segment containing only one epitope may not be able to generate a cytotoxic T cell response in a given individual if that individual does not possess an MHC molecule that can bind to the peptide. However, the presence of two different peptide epitopes increases the likelihood that at least one of the epitopes will be bound by an MHC molecule of the individual. Accordingly, the presence of a plurality of epitopes in the segments enhances the immunogenicity of the nucleic acid of the invention.

In response to the requirement for election of species, applicants elected a nucleic acid encoding a polypeptide containing the combination of the following four segments derived from four different HPV proteins: SEQ ID NO:66 (a segment of HPV 16 E6); SEQ ID NO:69 (a segment of HPV 16 E7); SEQ ID NO:152 (a segment of HPV 18 E6); and SEQ ID NO:154 (a segment of HPV 18 E7). The claims have been examined with respect to a nucleic acid encoding a hybrid polypeptide that contains these four segments. At page 9 of the Office Action, the

Examiner incorrectly referred to these segments as "epitopes." Rather than being an epitope (a peptide that binds to the binding groove of an MHC molecule or the antigen-binding region of an antibody), each of the segments contains a plurality of different peptide epitopes. Accordingly, the nucleic acid of the claimed invention encodes a hybrid polypeptide that contains one or more segments, each of which contains two or more peptide epitopes.

Contrary to the Examiner's assertions at page 8 of the Office Action, neither Hedley nor Urban discloses a nucleic acid that "encodes a hybrid polypeptide comprising a targeting signal sequence and polyepitopes of naturally occurring pathogenic proteins, wherein the epitopes are either contiguous or are separated by a spacer amino acid or spacer peptide."

Hedley describes microparticles and methods of preparing and using the microparticles. In some embodiments, the microparticles of Hedley contain a nucleic acid construct that encodes a polypeptide that includes an amino acid sequence essentially identical to an antigenic portion of a tumor antigen or a protein from an infectious agent. In general, the nucleic acid constructs of Hedley encode polypeptides that include a peptide of at least 7 amino acids in length that binds to an MHC class I or class II molecule. However, none of the nucleic acid constructs disclosed by Hedley encodes a hybrid polypeptide that contains a plurality of polyepitope portions of an HPV protein or any other protein of a pathogenic agent, as is required by the claimed invention. Instead, Hedley discloses several exemplary epitopes that can be encoded by a nucleic acid that is contained in the claimed microparticle.

Like Hedley, Urban describes an antigenic portion of a protein that can be included in a polypeptide encoded by a nucleic acid construct. In particular, Urban describes a 16 amino acid region of an HPV strain 16 E7 protein that can be encoded by such a nucleic acid construct. Urban does not described a hybrid polypeptide that contains a plurality of distinct epitope-rich portions of an HPV protein, as is required by the claimed invention.

It is applicants' understanding that Urban is cited in the present obviousness rejection as prior art under 35 U.S.C. § 102(e) (the Urban patent issued on February 6, 2001, which is after the filing date of the present application). In addition to the comments provided herein regarding the patentability of the claimed invention over the disclosure of Urban, 35 U.S.C. § 103(c) disqualifies Urban as prior art under 35 U.S.C. § 103/102(e) because Urban and the claimed

invention were, at the time the invention was made, both owned by Zycos Inc. (MPEP § 706.02(l)(1)).

The cited art does not render obvious a nucleic acid encoding a polypeptide containing the combination of HPV protein segments recited in SEQ ID Nos 66, 69, 152, and 154 (the elected species). As conceded by the Examiner at page 9 of the Office Action, neither Hedley nor Urban (the primary references) discloses a nucleic acid encoding a polypeptide containing the four HPV protein segments of SEQ ID NO:66, 69, 152, and 154. To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the teachings. In addition, the prior art references when combined must teach or suggest all of the claimed limitations. Neither of these requirements for a *prima facie* case of obviousness has been met by the present rejection.

A person of ordinary skill in the biological arts would not have been motivated to modify the nucleic acid compositions and immunization methods of Hedley and Urban to construct and use a nucleic acid that encodes a hybrid polypeptide containing the specific amino acid sequences selected by the Examiner from the several secondary references. Furthermore, even if one were to select the specific amino acid sequences identified by the Examiner and combine them in a chimeric polypeptide, such a combination would not result in the claimed invention.

Boursnell describes viral vectors encoding polypeptides that contain full length HPV proteins or antigenic portions thereof. The presently claimed nucleic acids require that the encoded hybrid polypeptide not include full length, intact E6 or E7 proteins. Accordingly, any combination of the various full length constructs of Boursnell would not result in the claimed invention. With respect to the combination of antigenic portions of HPV proteins, Boursnell gives no indication as to any specific portions of HPV proteins that would be desirable for combination into a chimeric polypeptide. In particular, Boursnell nowhere describes specific portions of HPV proteins (e.g., the segments represented by SEQ ID Nos 66, 69, 152, and 154) that contain a plurality of peptide epitopes, as is required by the segments contained in the hybrid polypeptides encoded by the claimed nucleic acids. Applicants' disclosure teaches that SEQ ID Nos 66, 69, 152, and 154 each contain multiple MHC-binding peptides, thus making these segments particularly suitable in combination for generating an anti-HPV immune response in an

individual. In addition to a lack of guidance regarding portions of HPV proteins that can be included in a chimeric polypeptide, Boursnell nowhere suggests linking a signal sequence to specific epitope-rich portions of HPV proteins, as is required by several of the pending claims.

According to the Examiner, the additional secondary references of Edwards, Dillner, and Bleul disclose "immunoreactive HPV epitopes" (see page 9 of Office Action), which a skilled artisan would have been motivated to combine into a single chimeric polypeptide. First, applicants clarify that an "epitope" (as used in the present application) is a peptide that binds to the binding groove of an MHC class I or class II molecule or to the antigen-binding region of an antibody (see specification at page 2, lines 23-25). The four amino acid sequences identified by the Examiner in Edwards, Dillner, and Bleul constitute fragments of HPV proteins that are, at least in some cases, clearly not "epitopes" as the term is used in the claimed invention. At least some of the amino acid sequences of Edwards, Dillner, and Bleul are much too long to bind to the binding groove of an MHC class I or class II molecule or to the antigen-binding region of an antibody. Second, aside from at least some of these protein fragments not constituting epitopes, a person of ordinary skill in the biological arts would have had no motivation to select these specific sequences and combine them into a single hybrid polypeptide. The HPV protein fragments described in the secondary references contain amino acid sequences at their amino and/or carboxy termini that are not contained in SEQ ID Nos 66, 69, 152, and 154. A skilled artisan would have had no motivation to piece together these different proteins fragments. The cited references provide no suggestion for such a combination. It is applicants' disclosure, not the cited art, that describes specific, shorter sequences as containing a plurality of epitopes and thus being useful for generating an immune response. Clearly, a skilled artisan would have had no reason to piece together *every* large HPV protein fragment that had been described in the prior art. Third, even if the four amino acid sequences identified by the Examiner in Edwards, Dillner, and Bleul were combined into a single chimeric polypeptide, such a combination would not result in the claimed invention. SEQ ID NO:2 of Bleul lacks the carboxy terminal 13 amino acids of SEQ ID NO:152. Accordingly, applicants submit that the cited references do not render the claimed invention obvious and therefore request that the Examiner withdraw the rejection.

Obviousness Type Double Patenting

On pages 10-11 of the Office Action; the Examiner rejected claims 1-66, 68, and 69 under the judicially created doctrine of obviousness type double patenting as allegedly unpatentable over claims 1-81 of Urban taken with either Boursnell and Hedley or Boursnell, Hedley, Edwards, Dillner, and Bleul. The present obviousness type double patenting rejects the claims based on the same references and on similar grounds as in the 35 U.S.C. § 103 rejection above.

Urban does not disclose a nucleic acid encoding a polypeptide containing the four HPV protein segments of SEQ ID NO:66, 69, 152, and 154. As summarized above in the response to the obviousness rejection, a person of ordinary skill in the biological arts would not have been motivated to modify the nucleic acid compositions and immunization methods of Urban to construct and use a nucleic acid that encodes a hybrid polypeptide containing the specific amino acid sequences selected by the Examiner from the several secondary references. Furthermore, even if one were to combine the specific amino sequences selected by the Examiner from the secondary references, such a combination would not result in the claimed invention. In light of these comments, applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are now in condition for allowance, which action is requested.

Attached is a marked-up version of the changes being made by the current amendments. The attached page is captioned "Version with Markings to Show Changes Made." Also attached is a listing of the claims pending upon entry of the amendments presented herein.

Enclosed is a Petition for Three Month Extension of Time and a check for the extension fee. Please apply any other charges (or credits) to Deposit Account No. 06-1050, referencing Attorney Docket No. 08191-013001.

Respectfully submitted,

Date: October 24, 2002

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Version with Markings to Show Changes Made

In the Claims:

Claims 45 and 67 have been cancelled without prejudice.

Claims 1, 5, 47, and 52 have been amended as follows:

1. (Amended) A nucleic acid encoding a hybrid polypeptide comprising a signal sequence and three segments, wherein the three segments are either contiguous or are separated by a spacer amino acid or spacer peptide:

(a) the first segment having the amino acid sequence of a first portion of a [naturally occurring tumor antigen or] naturally occurring protein of a pathogenic agent, the first segment being at least eleven amino acids in length and comprising two epitopes;

(b) the second segment having the amino acid sequence of a second portion of a [naturally occurring tumor antigen or] naturally occurring protein of a pathogenic agent, the second segment being at least eleven amino acids in length and comprising two epitopes different from the epitopes of (a); and

(c) the third segment having the amino acid sequence of a third portion of a [naturally occurring tumor antigen or] naturally occurring protein of a pathogenic agent, the third segment being at least eleven amino acids in length and comprising two epitopes different from the epitopes of (a) and (b),

provided that either

(i) the first, second and third portions are non-contiguous portions of the same naturally occurring protein, and the sum of all three portions constitutes less than 70% of the sequence of the naturally occurring protein; or

(ii) the first, second and third portions are portions of three different [naturally occurring tumor antigens or] naturally occurring proteins of one or more pathogenic agents.

5. (Amended) The nucleic acid of claim 1, further comprising

(d) a fourth segment which has the amino acid sequence of a fourth portion of a [naturally occurring tumor antigen or] naturally occurring protein of a pathogenic agent, the fourth segment

being at least eleven amino acids in length and comprising two epitopes different from the epitopes of (a), (b) and (c).

47. (Amended) A DNA encoding a hybrid polypeptide the sequence of which comprises at least one of the following segments of HPV strain 16 E6:

AMFQDPQERPRKLPQLCTEL (SEQ ID NO:64),

LLRREVYDFAFRDLCIVYRDGNPY (SEQ ID NO:65), and

KISEYRHYCYSLYGTTLEQQYNK (SEQ ID NO:66);

at least one of the following segments of HPV strain 16 E7:

TLHEYMLDLQPETTDLYSY (SEQ ID NO:67),

QAEPDRAHYNIVTF (SEQ ID NO:68), and

LLMGTLGIVCPICSQKP (SEQ ID NO:69);

at least one of the following segments of HPV strain 18 E6:

RRPYKLPDLCTELNTSLQDIEITCVYCKTVLELTEVFEFAFK (SEQ ID NO:152),

and

SVYGDTLEKLTNTGLYNLLIRCLRCQK (SEQ ID NO:153),

and at least one of the following segments of HPV strain 18 E7:

KATLQDIVLHLEPQNEIPV (SEQ ID NO:154),

HTMLCMCCKCEARI (SEQ ID NO:155), and

AFQQLFLNTLSFVCPWC (SEQ ID NO:156),

provided that the hybrid polypeptide does not comprise a sequence identical to the sequence of either full length, intact E6 or full length, intact E7 protein from HPV strain 16 or 18.

52. (Amended) A DNA encoding a hybrid polypeptide the sequence of which comprises a signal sequence and at least one of the following segments of HPV E6 and E7 proteins:

AMFQDPQERPRKLPQLCTEL (SEQ ID NO:64),

LLRREVYDFAFRDLCIVYRDGNPY (SEQ ID NO:65),

KISEYRHYCYSLYGTTLEQQYNK (SEQ ID NO:66),

TLHEYMLDLQPETTDLYSY (SEQ ID NO:67),

QAEPDRAHYNIVTF (SEQ ID NO:68),

RRPYKLPDLCTELNTSLQDIEITCVYCKTVLELTEVFEFAFK (SEQ ID NO:152),

SVYGDTLEKLTNTGLYNLLIRCLRCQK (SEQ ID NO:153),

KATLQDIVLHLEPQNEIPV (SEQ ID NO:154),

HTMLCMCCKCEARI (SEQ ID NO:155), and

AFQQLFLNTLSFVCPWC (SEQ ID NO:156);

provided that the hybrid polypeptide does not comprise a sequence identical to the sequence of either full length, intact E6 or full length, intact E7 protein from HPV strain 16 or 18.